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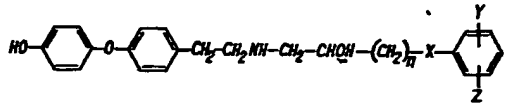
(19)

(54) THYRONAMINE DERIVATIVES

(71) We, ROUSSEL UCLAF, a French Body Corporate, of 35 Boulevard des Invalides, Paris, France, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

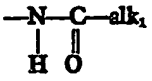
The present invention relates to novel thyronamine derivatives having useful pharmacological properties.

According to one feature of the present invention we provide compounds of general formula:—



(I)

[wherein n represents an integer from 1 to 4, X represents an oxygen or sulphur atom, and Y and Z, which may be the same or different and which may be in any desired positions on the benzene ring, each represent a hydrogen atom, an alkyl radical containing 1 to 6 carbon atoms, an alkenyl radical containing 2 to 6 carbon atoms, an alkoxy radical containing 1 to 6 carbon atoms, an acyl radical containing 2 to 6 carbon atoms, or a radical of formula



(wherein alk_1 represents an alkyl radical containing 1 to 6 carbon atoms)] and non-toxic acid addition salts thereof.

When Y or Z in formula I above represents a C_{1-6} alkyl radical, it is preferably a methyl, ethyl n - propyl, isopropyl, n - butyl or isobutyl radical. When Y or Z in formula I above represents a C_{2-6} alkenyl radical, it is preferably a vinyl or allyl radical. When Y or Z in formula I above represents a C_{1-6} alkoxy radical, it is preferably a methoxy, ethoxy or propoxy radical. When Y or Z in formula I above represents a C_{2-6} acyl radical, it is preferably an acetyl, propionyl or butyryl radical. When Y or Z in formula I above represents a radical of formula —NH—CO—alk_1, it is preferably an acetyl-, propionyl- or butyryl-amino radical.

Preferred classes of compounds of formula I above include those wherein X represents an oxygen atom, those wherein n represents the number 1 and those wherein Y and Z represent a hydrogen atom, as well as the non-toxic acid addition salts of such compounds.

The reference herein to "non-toxic acid addition salts" means those acid addition salts of compounds of formula I, the anionic moieties of which are physiologically compatible at the dosages at which the salts are administered.

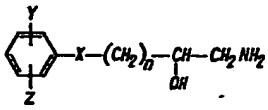
The compounds of formula I and their acid addition salts have spasmolytic properties and especially a cardiovascular activity of the positive inotropic type. Thus, for example, from experiments which we have carried out we have found that compounds of formula I (particularly N - [β - hydroxy - γ - phenoxy - propyl] - 4 - [p - hydroxyphenoxy] - phenyl - ethylamine) have an advantageous positive inotropic effect as compared with thyronamine, i.e. 4 - [p - hydroxyphenoxy] - phenyl - ethylamine. The compounds can thus be used for example, for strengthening cardiac contraction, stimulating the use of energy in the myocardium and improving coronary output. These properties render the compounds useful in human or animal medicine e.g. for treating coronary deficiencies, cardiac deficiencies and arrhythmia.

According to a further feature of the present invention therefore we provide pharmaceutical and veterinary compositions comprising, as active ingredient, at least one compound of formula I and/or at least one non-toxic acid

addition salt thereof together with at least one pharmaceutical carrier or excipient. N - [β - hydroxy γ - phenoxypropyl]4 - [p - hydroxyphenoxy]phenethylamine and its non-toxic acid addition salts, and N - [β - hydroxy γ(o - allylphenoxy)propyl]4 - [p - hydroxyphenoxy]phenethylamine and its non-toxic acid addition salts, are preferred compounds according to the invention having particularly useful properties of the kind referred to.

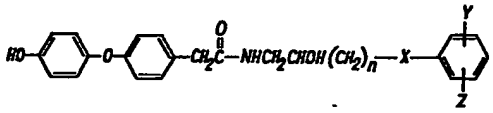
Examples of such non-toxic acid addition salts include those derived from such mineral acids as hydrochloric, hydrobromic, hydriodic, nitric, sulphuric and phosphoric acid, and such carboxylic acids as acetic, maleic, fumaric, succinic, tartaric, citric or benzoic acid, as well as sulphonic acids such as methanesulphonic acid or paratoluenesulphonic acid.

According to a further feature of the present invention we provide a process for preparing compounds of formula I (as hereinbefore defined) which comprises reacting p - (p - hydroxyphenoxy)phenylacetic acid (or a functional derivative thereof) with an amine of formula



(II)

(wherein X, Y, Z and n are as hereinbefore defined) to obtain a compound of formula



(III)

(wherein X, Y, Z and n are as hereinbefore defined) which is reduced to produce a compound of formula I (as hereinbefore defined).

If desired, the reaction of the compound of formula II with the acid (or functional derivative thereof) may be effected at an elevated temperature.

The above-mentioned functional derivative of p - (p - hydroxyphenoxy)phenylacetic acid may be for example the anhydride, a mixed anhydride, acid chloride or a lower alkyl ester. When a lower alkyl ester is used, the reaction may be effected by simply heating the ester with the amine. When the acid chloride or the anhydride is used, the reaction may be carried out, for example, in an inert solvent, such as an aromatic hydrocarbon (e.g. benzene, xylene or toluene), chloroform or diethyl ether.

When a mixed anhydride is used, it is preferably an anhydride of p - (p - hydroxyphenoxy)phenylacetic acid and a carboxylic acid containing 1 to 6 carbon atoms. This mixed anhydride, which is reacted with the amine of formula II, e.g. in a solvent such as acetone, may be prepared by reacting an alkyl chloroformate with a salt of p - (p - hydroxyphenoxy)phenylacetic acid, for example the triethylamine salt.

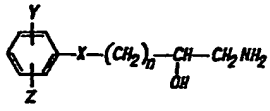
In a preferred embodiment of the process of the invention, the compounds of formula I are prepared by adding the said acid to the amine of formula II to form a salt which is dehydrated by simple heating to form the amide of formula III. Reduction of the compound of formula III is preferably effected using lithium aluminium hydride in the presence of aluminium chloride.

The non-toxic acid addition salts of the compounds of formula I may be prepared for example by reacting a compound of formula I with an appropriate acid. By means of the above-described process of the invention, the following new intermediates, can be prepared;

N - [β - hydroxy γ - phenoxypropyl]4 - [p - hydroxyphenoxy]phenylacetamide and

N - [β - hydroxy γ(o - allylphenoxy)-propyl]4 - [p - hydroxyphenoxy]phenylacetamide.

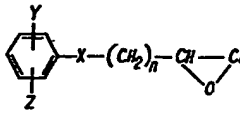
The compounds of formula:—



(II)

(wherein X, Y, Z and n are as defined above), are generally known and may be prepared, for example, according to the process described by M. S. Malinovskii and Col. ZH. Org. Khim. 1(8) 1365—7 (1965) or according to the method indicated in C.A. *72* 12342 n (1970).

According to a still further feature of the present invention we provide a process for the preparation of compounds of formula I (as hereinbefore defined) which comprises reacting 4 - [p - hydroxy - phenoxy]phenyl - ethylamine with a compound of formula IV:—



(IV)

(wherein X, Y, Z and n are as hereinbefore

defined) to obtain a compound of formula I (as hereinbefore defined).

In a preferred embodiment, of the last-mentioned process, the condensation reaction between 4 - [p - hydroxy - phenoxy] - phenyl - ethylamine and the compound of formula IV is effected in an organic solvent such as dimethylformamide, and at a temperature between 100 and 200°C, preferably about 150°C. The compounds of formula IV used at the start of the process of the invention are generally known and may be prepared, for example, according to the method of Werner (Rec. Soc. Chim. PB *67*, 442, (1948).

The compositions according to the invention may be administered by the oral, rectal or transcutaneous route, e.g. in the form of tablets, cachets, capsules, emulsions, syrups, orally ingestible solutions, suppositories and injectable solutions or suspensions. Such compositions may be prepared in conventional manner.

The preferred dosage of active ingredient may vary depending on the subject, the route of administration and the condition being treated, but may be, for example, 10 mg to 60 mg per day for injection in an adult.

The following Examples illustrate the invention.

Example 1

N - [β - hydroxy γ - phenoxypropyl]4 - [p - hydroxyphenoxy]phenyl - ethylamine hydrochloride:

Step A: **N - (β - hydroxy γ - phenoxypropyl)4 - (p - hydroxyphenoxyphenylacetamide:**

7.4 g of 2 - hydroxy 3 - phenoxypropylamine are dissolved hot in 74 cm³ of ethyl acetate. A solution containing 10 g of p - (p - hydroxyphenoxy)phenylacetic acid in 100 cm³ of ethyl acetate is poured into the solution obtained. The solution thus obtained is refluxed for ten minutes, cooled, the crystals obtained are filtered off and washed. 14.5 g of crystals, melting at 108°C, are thus obtained. These crystals are slowly heated to about 200°C and kept at 200°C for one hour, with agitation. They are left to cool to ambient temperature, taken up in methanol, then 1 g of active charcoal is added and the mixture is refluxed, filtered and evaporated at reduced pressure. In this way, 10 g of N - [β - hydroxy γ - phenoxypropyl]4 - (p - hydroxyphenoxy)phenylacetamide, m.p. 130°C, are obtained, which are used as such in the following step.

Step B: **N - [β - hydroxy γ - phenoxypropyl]4 - [p - hydroxyphenoxy]-phenylethylamine hydrochloride:**

2.1 g of lithium aluminium hydride are added to 40 cm³ of tetrahydrofuran. The mixture thus obtained is cooled and 2.1 g of aluminium chloride are added. Then a solution containing 4.2 g of the product prepared in Step A in 80 cm³ of tetrahydrofuran is added. The mixture is refluxed for two hours. The reaction mixture is cooled and the excess hydride is hydrolysed with tetrahydrofuran containing 10% water. Then, a saturated solution of sodium potassium tartrate is added dropwise. The precipitate is filtered off, washed and the filtrate is concentrated to dryness. Then, ethyl acetate, followed by saturated ethyl acetate in hydrochloric acid, are added to the residue. The mixture is filtered, concentrated, and the precipitate formed is washed. Thus 2.8 g of N - [β - hydroxy γ - phenoxypropyl]4 - [p - hydroxyphenoxy]phenylethylamine are obtained, m.p. 138°C.

Example 2

N - [β - hydroxy γ - phenoxypropyl]4 - [p - hydroxyphenoxy]phenylethylamine hydrochloride:

1.1 g of thyronamine, i.e. 4 - [p - hydroxyphenoxy]phenylethylamine, are added to 5.5 cm³ of dimethylformamide. To this solution are added 800 mg of 1,2 - epoxy 3 - phenoxypropane (prepared according to the method indicated by Fourneau Bull. Soc. Chim. *5*, 229 (1909)). The reaction temperature is kept at 160°C for three hours, with agitation. The mixture is allowed to cool to ambient temperature, and 10 cm³ of a saturated solution of hydrochloric acid in ethyl acetate are added. The solvents are concentrated at reduced pressure, the mixture is taken up in methyl alcohol, 0.5 g of active charcoal are added and the mixture is refluxed. It is filtered, the filtrate is concentrated and 10 cm³ of anhydrous ether are added. The mixture is left to stand at ambient temperature for three hours. It is filtered, and the crystals obtained are washed, and recrystallisation from isopropanol is effected. 400 mg of N - [β - hydroxy γ - phenoxypropyl]4 - [p - hydroxyphenoxy]phenylethylamine hydrochloride are obtained, m.p. 136°C.

Example 3

N - [β - hydroxy γ - (o - allylphenoxy)-propyl]4 - (p - hydroxyphenoxy)phenethylamine hemisuccinate:

Proceeding as in Example 1, starting from 4 - (p - hydroxyphenoxy)phenylacetic acid and 2 - hydroxy 3 - (o - allylphenoxy)propylamine (prepared as indicated in C.A. *72* 12342 n 1970), N - [β - hydroxy γ(o - allylphenoxy)propyl]4 - [p - hydroxyphenoxy]-phenylacetamide is obtained, which is then reacted with lithium aluminium hydride to obtain N - [β - hydroxy γ(o - allylphenoxy)-propyl]4 - (p - hydroxyphenoxy)phenylethylamine, which is reacted with succinic acid in order to form the hemisuccinate, m.p. 138°C.

Analysis: $C_{29}H_{33}NO_6$=478.570
Calculated: C% 70.27 H% 6.76 N% 2.93
Found: C% 70.10 H% 7.0 N% 2.8

Product of Example 1 or 2		20 mg
Sodium chloride		1275 mg
Distilled water	q.s.p.	150 cm³

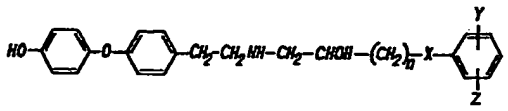
Example 4

Pharmaceutical compositions:

An injectable form, for parenteral injection was prepared:

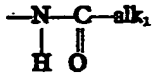
WHAT WE CLAIM IS:—

1. Compounds of general formula:—



(I)

[wherein n represents an integer from 1 to 4, X represents an oxygen or sulphur atom, and Y and Z, which may be the same or different and which may be in any desired positions on the benzene ring may each represent a hydrogen atom, an alkyl radical containing 1 to 6 carbon atoms, an alkenyl radical containing 2 to 6 carbon atoms, an alkoxy radical containing 1 to 6 carbon atoms, an acyl radical containing 2 to 6 carbon atoms, or a radical of formula



(wherein alk_1 represents an alkyl radical containing 1 to 6 carbon atoms)] and non-toxic acid addition salts thereof.

2. Compounds as claimed in claim 1 wherein X represents an oxygen atom.

3. Compounds as claimed in claim 1 or claim 2 wherein n represents the number 1.

4. Compounds as claimed in any of claims 1 to 3 wherein at least one of the symbols Y and Z represents a hydrogen atom.

5. Compounds as claimed in any of claims 1 to 3 wherein at least one of the symbols Y and Z represents a methyl, ethyl, n - propyl, iso - propyl, n - butyl or iso - butyl group.

6. Compounds as claimed in any of claims 1 to 3 wherein at least one of the symbols Y and Z represents a methoxy, ethoxy, or propoxy group.

7. Compounds as claimed in any of claims 1 to 3 wherein at least one of the symbols Y and Z represents a vinyl or allyl group.

8. Compounds as claimed in any of claims 1 to 3 wherein at least one of the symbols Y and Z represents an acetyl, propionyl or butyryl group.

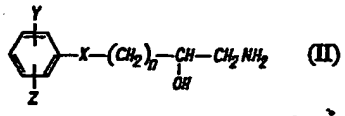
9. Compounds as claimed in any of claims 1 to 3 wherein at least one of the symbols Y and Z represents an acetyl-, propionyl- or butyryl-amino group.

10. N - [β - hydroxy γ - phenoxypropyl]4 - [p - hydroxyphenoxy]phenylethylamine.

11. N - [β - hydroxy γ(o - allylphenoxy)-propyl]4 - [p - hydroxyphenoxy]phenylethylamine.

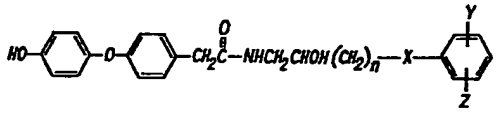
12. Compounds of formula I as claimed in any of the preceding claims in the form of their acid addition salts with hydrochloric, hydrobromic, hydriodic, nitric, sulphuric, phosphoric, acetic, maleic, fumaric, succinic, tartaric, citric, benzoic, methanesulphonic or p - toluene - sulphonic acid.

13. A process for preparing compounds of formula I (as defined in claim 1) which comprises reacting p - (p - hydroxyphenoxy)-phenylacetic acid (or a functional derivative thereof) with an amine of formula:



(II)

(wherein X, Y, Z and n are as defined in claim 1) to obtain a compound of formula:



(III)

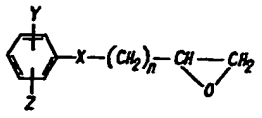
(wherein X, Y, Z and n are as defined in claim 1) which is reduced to produce a compound of formula I (as defined in claim 1).

14. A process as claimed in claim 13 wherein the amine of formula II is reacted with the anhydride, a mixed anhydride, the acid chloride or a lower alkyl ester of p - (p - hydroxyphenoxy)phenylacetic acid.

15. A process as claimed in claim 14 wherein the mixed anhydride is an anhydride of p - (p - hydroxyphenoxy)phenylacetic acid and a carboxylic acid containing 1 to 6 carbon atoms.

16. A process for the preparation of compounds of formula I (as defined in claim 1) which comprises reacting 4 - [p - hydroxy -

phenoxy] - phenyl - ethylamine with a compound of formula IV:—



(IV)

(wherein X, Y, Z and n are as defined in claim 1) to obtain a compound of formula I (as defined in claim 1).

17. A process as claimed in claim 16 wherein the reaction is effected at a temperature of 100° to 200°C.

18. A process for the preparation of non-toxic acid addition salts of compounds of formula I (as defined in claim 1) which comprises reacting a compound of formula I with an appropriate acid.

19. A process for the preparation of compounds of formula I (as defined in claim 1) substantially as herein described.

20. A process for the preparation of compounds of formula I (as defined in claim 1) substantially as herein described with reference to any of Examples 1 to 3.

21. Compounds of formula I (as defined in claim 1) and non-toxic acid addition salts thereof whenever prepared by a process as claimed in any of claims 13 to 20.

22. Pharmaceutical and veterinary compositions comprising, as active ingredient, at least one compound of formula I (as defined in claim 1) and/or at least one non-toxic acid addition salt thereof together with at least one pharmaceutical carrier or excipient.

23. Compositions as claimed in claim 22 wherein the active ingredient comprises a compound as claimed in claim 10 and/or a non-toxic acid addition salt thereof.

24. Compositions as claimed in claim 22 wherein the active ingredient comprises a compound as claimed in claim 11 and/or a non-toxic acid addition salt thereof.

25. Compositions as claimed in any of claims 22 to 24 in the form of tablets, cachets, capsules, emulsions, syrups, orally ingestible solutions, suppositories or injectable solutions or suspensions.

26. Compositions as claimed in claim 22 substantially as herein described.

27. Compositions as claimed in claim 22 substantially as herein described with reference to Example 4.

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